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Perspective

Nodding syndrome—a new hypothesis and new direction for research

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SUMMARY

Nodding syndrome (NS) is an unexplained neurological illness that mainly affects children aged between 5 and 15 years. NS has so far been reported from South Sudan, northern Uganda, and Tanzania, but in spite of extensive investigations, the aetiology remains unknown. We hypothesize that blackflies (Diptera: Simuliidae) infected with *Onchocerca volvulus* microfilariae may also transmit another pathogen. This may be a novel neurotropic virus or an endosymbiont of the microfilariae, which causes not only NS, but also epilepsy without nodding. This hypothesis addresses many of the questions about NS that researchers have previously been unable to answer. An argument in favour of the hypothesis is the fact that in Uganda, the number of new NS cases decreased (with no new cases reported since 2013) after ivermectin coverage was increased and with the implementation of a programme of aerial spraying and larviciding of the large rivers where blackflies were breeding. If confirmed, our hypothesis will enable new strategies to control NS outbreaks.

1. Introduction

Nodding syndrome (NS) is an unexplained neurological illness that has so far been reported from South Sudan, northern Uganda, and Tanzania.[1] NS mainly occurs in children aged between 5 and 15 years. The first clinical symptom is often an involuntary nodding of the head in a previously healthy child. Other types of epileptic seizures may follow, which in some children are accompanied by cognitive deterioration and stunted growth, leading to dwarfism and the absence of development of secondary sexual characteristics.[1]

Various infectious, toxic, nutritional, psychosocial, and genetic causes have been proposed, but none have been confirmed. However, there appears to be a link between NS and onchocerciasis. NS is only known to occur in onchocerciasis endemic areas, and case–control studies have demonstrated a higher prevalence of onchocerciasis in individuals with NS than in controls.[1] A high prevalence of epilepsy has also been described in many onchocerciasis endemic areas,[2] and higher microfilarial loads have been found in skin snips of onchocerciasis patients with epilepsy than in those without.[3] PCR tests on the cerebrospinal fluid (CSF) of NS patients have failed to identify *Onchocerca volvulus* DNA,[4,5] but these results are difficult to interpret as they may have been complicated by previous treatment with ivermectin.[6] However, because *O. volvulus* microfilariae are not known to invade the brain, it is difficult to understand how *O. volvulus* could directly cause the neurological damage seen in NS patients.

We therefore propose the aetiological hypothesis below.

2. Hypothesis

The association between NS and onchocerciasis may be explained by the existence of a common vector – blackflies (*Simulium* spp – transmitting *O. volvulus*) and a second pathogen involved in the aetiology of NS.

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Such a pathogen could, for example, be a neurotropic virus transmitted by blackflies co-infected with *O. volvulus* microfilariae. Many laboratory studies have shown that arboviral transmission is enhanced in mosquitoes and other Diptera that concurrently ingest microfilariae,[7,8] and the same could be true for blackflies. In mosquitoes, microfilariae penetrate the midgut and introduce the virus directly into the haemocoel, allowing them to become infectious more quickly than normal.[8] This has been demonstrated in experiments with *Aedes taeniorhynchus* co-infected with Rift Valley fever virus, and *Aedes aegypti* co-infected with dengue virus type 2 and *Brugia malayi* microfilariae.[7] It was also found that the biting midge, *Culicoides nubeculosus*, became infectious after ingesting blue tongue virus and *Onchocerca cervicalis* microfilariae, but not after ingesting the virus alone.[9]

A pathogen could also be an endosymbiont of *O. volvulus* microfilariae, for example *Wolbachia* bacteria. *Wolbachia* are known to play a role in the pathogenicity of onchocerciasis.[10] Toxins secreted by *Wolbachia* are able to cause pruritus, skin inflammation, and ocular lesions.[10,11] However, we do not currently know how these toxins could damage the central nervous system (CNS) in the absence of microfilariae penetrating the brain.

The hypothesis of a new pathogen transmitted by blackflies addresses many of the questions about NS that researchers have previously been unable to answer, including those listed below.

2.1. Why is NS only present in a limited number of onchocerciasis endemic areas?

The distribution of NS could be limited by the distribution of an appropriate disease vector. It is possible that only certain (cyto)species of blackfly are able to transmit the pathogen. It is also possible that NS occasionally occurs in hypo- and mesoendemic areas for *O. volvulus*, but only becomes epidemic in areas that are hyperendemic for *O. volvulus*. An argument for the latter is supported by the high prevalence of epilepsy seen in many onchocerciasis hyperendemic areas, and that NS-like features have been reported in several other onchocerciasis hyperendemic areas in the past. In 1938, a Mexican physician described a syndrome in Chiapas and Oaxaca, Mexico, characterized by epileptic seizures, stunted growth, and mental retardation in patients with onchocerciasis.[12] In Mabira Forest, 60 km east of Kampala, Uganda, a 'Nakalanga syndrome' outbreak (a syndrome with symptoms similar to NS) was described in 1950.[13] NS-like features have also been reported in other onchocerciasis endemic areas in Liberia,[14] western Uganda,[15] Burundi,[16] and possibly the Central African Republic, Ethiopia, Mali,[17] and Cameroon.[18]

2.2. Why do NS epidemics appear and disappear?

An NS epidemic may appear in onchocerciasis hyperendemic areas when a non-immune population migrates to an area containing blackflies infected with an 'NS pathogen'. Population displacement resulting from civil conflict has preceded NS outbreaks in both northern Uganda and South Sudan. An NS epidemic may subsequently decrease with increasing herd immunity. It may also decrease with increasing ivermectin coverage. This will reduce the likelihood of blackflies becoming infected with microfilariae and therefore transmitting a pathogen. NS epidemics may be interrupted by insecticide or larvicide use against blackflies.

2.3. How can the current epidemiological situation in the three affected countries be explained?

2.3.1. Northern Uganda

Northern Uganda was engaged in a war with the Lord's Resistance Army between 1987 and 2008. About 1.8 million people in Gulu, Kitgum, and Pader districts were displaced into 'protective' internally displaced people camps, some for more than 15 years. Before displacement, frequent contact with blackfly-infested rivers had caused immunity in adults. Relief food was distributed in the camps and water was collected from boreholes resulting in less frequent contact with the rivers. As a result, children born in camps lacked immunity against the 'NS pathogen'. People were released from the camps from 2006 and non-immune children came into contact with infected blackflies at rivers near their home villages. There was no ivermectin distribution during the war, and community-directed treatment with ivermectin was only started in 2009, and in the villages most affected by NS, in 2012. A combined lack of immunity and the absence of an ivermectin distribution programme potentially resulted in the NS epidemic[19] (Figure 1).

A programme of aerial spraying and larviciding of the large rivers where blackflies were breeding was implemented in 2012. This was followed by a decrease in the incidence of NS, with no new cases officially reported in 2013.[20,21] The already decreasing trend of new NS cases before spraying took place could have been a consequence of the intensified ivermectin programme (biannual distribution).

2.3.2. South Sudan

Sudan used insecticides to control river blindness until autonomy in 1972, when spraying stopped due to a lack of funding. People fled into forests infested by blackflies during the Second Sudanese Civil War (1983–2005) and it is conceivable that because of insecticide spraying in the past, the population had limited immunity. The first cases of NS appeared around 1990[22] and the prevalence has been increasing since. The prevalence of NS in Mvolo county has been estimated at 8.4% by the South Sudan Relief and Rehabilitation Commission (4025 NS patients out of 48 100 people) (Anthony Amba; personal communication), which is a doubling of prevalence compared to the 2003 estimate of 4.6%.[23] There are still new NS cases occurring in South Sudan (Mr S.A. Komoyangi, Chair, Diko Community Development Committee, Western Equatoria State, South Sudan; personal communication). The reason for this might be the low ivermectin coverage (only distributed annually).

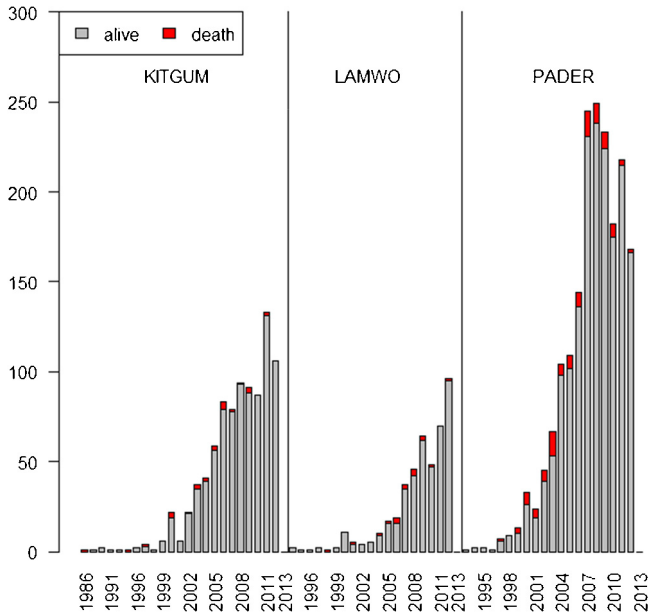

Figure 1. Number of new cases of nodding syndrome between 1997 and 2013 in the districts of Kitgum, Lamwo, and Pader, in northern Uganda.

2.3.3. Tanzania

Around 1850, the Wapogoro tribe fled from the Ulanga plains to isolated regions in the Mahenge mountains to avoid conflict with the Ngoni.[22] The prevalence of epilepsy in Mahenge was estimated to be 2% in 1970[24] and 1.8% in 1989.[25] Over the last 10 years, the incidence of NS has been low and stable.[26] Because insecticides and larvicides have never been used in Mahenge, we hypothesize that the population has been exposed to the 'NS pathogen' for a long time. The fact that NS is endemic in Mahenge may be explained by an increase in acquired immunity of the local population over a very long period and good ivermectin coverage.

2.4. Why are only children affected?

Many infectious disease epidemics show a predisposition for very young children. The onset of NS between the ages of 5 and 15 years is probably explained by the following: (1) protection of very young children by the antibodies of their mothers; (2) the fact that very young children are less likely to spend a lot of time near rivers; (3) the incubation time of the disease; (4) treatment with ivermectin is only started after the age of 5 years. If the pathogen is a microfilarial endosymbiont, then young children may be at particular risk of developing the disease. It is also possible that, similar to other viral childhood infections, the 'NS pathogen' could lead to immunity for life, explaining why adults rarely develop the disease.

2.5. Why are non-immune adults not developing NS?

It may be that the rate of infection in blackflies is low. In the event that the pathogen is a microfilarial endosymbiont, it may be that you need to become infected many times, similar to onchocerciasis, before you develop a serious disease. This could explain the low risk of disease development seen in occasional non-immune travellers who spend only a short time at the riverside.

2.6. How can the severe stunting (dwarfism) be explained?

Dwarfism could be caused by an infection with the 'NS pathogen' at an early age, when the child's brain is still developing. Hypothalamic-pituitary dysfunction has been described post-encephalitis[27] and a similar stunted growth and lack of secondary sexual characteristics has also been observed in perinatally HIV-infected children who survived up to 18 years without antiretroviral therapy,[28] and in perinatally human T-cell lymphotropic virus type 1 (HTLV-1)-infected children (K. Verdonck; personal communication). It is unlikely that the pronounced dwarfism is only caused by malnourishment because not all these children are particularly malnourished.

2.7. How should the CSF and brain magnetic resonance imaging (MRI) findings observed in patients with NS be interpreted?

The CSF of patients with NS is generally clear, with glucose and protein levels within normal limits.[1,4,29] In a viral CNS infection one would expect an increased cell count and an increased total protein level. However, in subacute sclerosing panencephalitis, CSF findings are usually acellular with a normal or mildly raised protein concentration.[30] Therefore normal CSF findings do not exclude a chronic or subacute viral infection. Brain MRI has only been performed in a limited number of patients with NS.[4,29,31] None of the patients showed evidence of meningeal or parenchymal inflammation, or a focal brain lesion caused by a parasitic infection. Five patients from Tanzania and two patients from Uganda had aspecific hippocampus abnormalities, and in five Ugandan patients, cerebral atrophy was noted.[1] Brain MRI do not provide evidence of a viral CNS infection, but also do not suggest a parasitic infection of the brain.

2.8. Can blackflies transmit pathogens?

Blackflies can transmit vesicular stomatitis New Jersey virus to cattle, horses, and swine.[32] There are no reports of blackflies transmitting arboviruses to humans. However with over 1700 *Simulium* species described worldwide, it is plausible that blackflies may transmit unidentified viruses from human and zoonotic origin.

3. Directions for future research

More precise incidence data on NS, epilepsy, and onchocerciasis in relation to blackfly distribution are required. At the same time, research should focus on the search for a new pathogen. Previous studies using multiplex PCR have not been able to identify a pathogen in the serum or CSF of NS patients.[33] However, such methods may not be able to detect a new pathogen and it is conceivable that once nodding appears, the 'NS pathogen' may no longer be detectable in serum or even CSF. The way forward is to plan a metagenomic study of blackflies, microfilariae, and human samples (preferably brain tissue).

In conclusion, NS may be caused by a new pathogen transmitted by blackflies. Similar to other vector-borne diseases, infection depends on a combination of the amount of exposure, percentage of insects carrying the pathogen, immunity, and chance. The burden of disease may be considerable, as the 'NS pathogen' may also cause epilepsy without nodding. The use of larvicides may be able to stop epidemics; however, if vector control is not sustained there may be an increase in clinical disease because of decreased immunity. Improving ivermectin coverage and increasing the frequency of its administration may reduce the capacity of the blackflies to transmit the pathogen. The planning of a clinical trial to evaluate these control strategies, either alone or in combination, should be considered.

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